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Claims

We claim;

1 1 A method of treating degenerative diseases due to

2 acquired mitochondrial DNA damage

3 redox damage to mitochondrial macromolecules

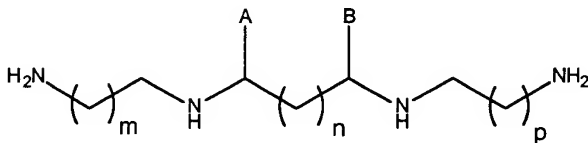
4 and inherited mitochondrial genetic defects

5 said method comprising the steps of: selecting a composition from a group consisting of open
6 ring polyamines, macrocyclic polyamines, branched linear polyamines and substituted
7 polyamines;

8 synthesizing said composition; and

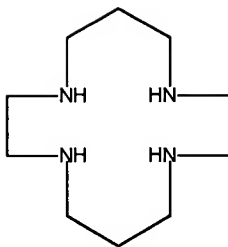
9 administering an effective dose of said composition to a mammal.

1 2 The method of Claim 1 wherein said step of synthesizing comprises converting by treatment
2 with an alkyl halide a compound taken from a group consisting of those compounds having the
3 formula

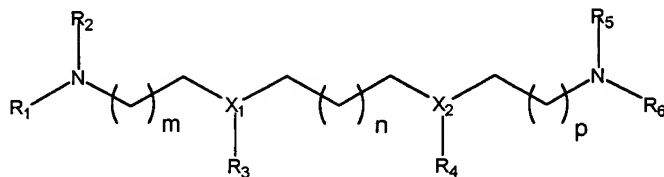


8 wherein A and B are hydrogen or alkyl, and m, n, and p are the same or different, and those
9 compounds having the formula

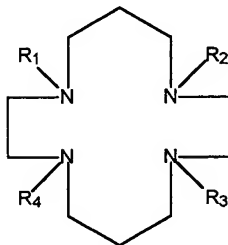
process of use
by process
of making



3 The method of claim 2 wherein said composition is taken from a group consisting of those compositions having the formulae:



and



wherein:

R₁ and R₂ are taken from a group consisting of hydrogen, alkyl, aryl, cycloalkyl, amino acid, glutathione, uric acid, ascorbic acid, taurine, estrogen, dehydroepiandrosterone, probucol, vitamin E, hydroxytoluene, carvidilol, α-lipoic acid, α-tocopherol, ubiquinone, phyloquinone, β-carotene, meanadione, glutamate, succinate, acetyl-L-carnitine, co-enzyme Q, lazeroids, polyphenolic flavonoids, homocysteine, menaquinone, idebenone, dantrolene, – (CH₂)_n[XCH₂]_nNH₂ - wherein n = 3-6 and R₁ and R₂ taken together are –(CH₂XCH₂)_n- wherein n = 3-6,

R₃ and R₄ are taken from a group consisting of hydrogen, alkyl, aryl, cycloalkyl, amino acid, glutathione, uric acid, ascorbic acid, taurine, estrogen, dehydroepiandrosterone, probucol, vitamin E, hydroxytoluene, carvidilol, α-lipoic acid, α-tocopherol, ubiquinone, phyloquinone, β-carotene, meanadione, glutamate, succinate, acetyl-L-carnitine, co-enzyme Q, lazeroids, polyphenolic flavonoids, homocysteine, menaquinone, idebenone, dantrolene or heterocycle and R₃ and R₄ taken together are –(CH₂XCH₂)_n- wherein n = 3-6,

R₅ and R₆ are taken from a group consisting of hydrogen, alkyl, aryl, cycloalkyl, amino acid, glutathione, uric acid, ascorbic acid, taurine, estrogen, dehydroepiandrosterone, probucol, vitamin E, hydroxytoluene, carvidilol, α-lipoic acid, α-tocopherol, ubiquinone, phyloquinone, β-carotene, meanadione, glutamate, succinate, acetyl-L-carnitine, co-enzyme Q, lazeroids, polyphenolic flavonoids, homocysteine, menaquinone, idebenone, dantrolene – (CH₂)_n[XCH₂]_nNH₂ - wherein n = 3-6, and R₅ and R₆ taken together are –(CH₂XCH₂)_n- wherein n = 3-6.

M, n, and p may be the same or different and are bridging groups of variable length from 3-12 carbons, and

X is taken from a group consisting of nitrogen, sulfur, phosphorous and carbon.

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4 The method of Claim one wherein said step of synthesizing further comprises the steps of:

- admixing an element taken from a group consisting of 2,4 dibromopropane and absolute ethanol into 1,2-diaminoethane hydrate;
- heating the resulting mixture to approximately 50°C for about one hour;
- adding potassium chloride;
- continuing said heating for three hours;
- filtering potassium bromide out of the mixture;
- distilling the mixture at reduced pressure;
- allowing the formation of top and bottom layers;
- separating and distilling the top layer;
- converting free amine in the distilled top layer to a tetrahydrochloride salt; and
- converting said salt to a free amine by treatment with ammonium hydroxide.

5 The method of claim 4 wherein said step of converting to a tetrahydrochloride salt comprises adding hydrochloric acid to said distilled top layer.

6 The method of Claim 4 wherein said composition consists of 1,3-bis-[(2'-aminoethyl)-amino]propane and step of admixing a solution comprises preparing said solution by mixing 1,3-dibromopropane and absolute ethanol in a ratio of approximately 1 to 3 per weight.

7 The method of Claim 6 wherein said step of admixing further comprises slowly adding said solution into 1,2-diaminoethane hydrate in a ratio of approximately 2.6 to 1 per weight.

1 8 The method of claim 7 wherein, the step of preparing said solution comprises mixing 15
2 grams of 1,3-diaminopropane and 50 milliliters of absolute ethanol; and
3 the step of slowly adding comprises adding said solution to 20 grams of potassium chloride;

1 9 The method of Claim 8 wherein said step of converting to a tetrahydrochloride salt
2 comprises adding six molar concentration of hydrochloric acid.

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1 10 The method of claim 2 wherein said step of selecting comprises:
2 ascertaining the heats of formation of a set of said compounds; and choosing said compound in
3 consideration of its heat of formation compared to the heats of formation of other compounds
4 in said set.

1 11 The method of claim 10 wherein: said step of ascertaining comprises: calculating the heats
2 at the formation of said set of compounds from their respective constituent atoms.

1 12 The method of claim 11 wherein said step of choosing comprises determining the
2 stabilities of said set of compounds as a function of their respective heats of formation;
3 wherein said stabilities are determined in inverse proportion to said respective heats of
4 formation; and
5 whereby the relative stabilities of the set of compounds are deemed indicative of ability to
6 yield the most stable complex when reacted with a group of metals.

1 13 The method of Claim 12 wherein;
2 said group of metals includes copper, cobalt, iron, zinc, cadmium, manganese and chromium.

1 14 The method of Claim 13 wherein said degenerative diseases comprise neurodegenerative
2 diseases characterized by excess iron pools and said compound is selected from a group
3 consisting of 2,2,2-piperidine and 2,3,2 adamantane.

1 15 The method of Claim 13 wherein said degenerative diseases comprise ischemic damage
2 and pump failure post myocardial infarction characterized by iron-induced toxic redox effects
3 and depletion of tissue zinc stores; and said compound is selected from a group consisting of
4 zinc cyclam methylated, zinc cyclam adamantane, cyclam methylated and cyclam adamantane.


1 16 The method of Claim 13 wherein said degenerative diseases comprise neurodegenerative
2 diseases and strokes; and said composition is selected from a group consisting of compositions
3 having open ring metal binding molecules taken from a group consisting of compositions
4 having copper binding molecules and manganese binding molecules.

1 17 The method of Claim 16 wherein said compositions having copper-binding molecules
2 include 2,3,2 isopropyl on N1/N4; and
3 said compositions having manganese-binding molecules include 3,3,3 tetramine.

1 18 The method of claim 13 wherein said degenerative diseases comprise neurodegenerative
2 disorders, stroke, glaucoma, atherosclerosis, cardiomyopathy, ischemia, optic neuropathy,
3 peripheral neuropathy, presbycusis and cancer; and said composition is selected from
4 derivatives of those compounds having the largest ring molecules.

1 19 The method of claim 18 wherein said compounds having the largest ring molecules
2 includes 3,3,3 tetramine, cyclam adamantanes, cyclam 3,3,3 and compounds having alkyl
3 substituted molecules.

1 20 The method of Claim 13 wherein said degenerative diseases comprise Parkinson's, Lou
2 Gehrig's, Binswanger's, and Lewy Body diseases, Olivopontine Cerebellar Degeneration,
3 stroke, glaucoma and optic neuropathy; and
4 said composition is selected from a group of compositions having alkyl side chains.

1 21 The method of Claim 13 wherein said degenerative diseases comprise neurodegenerative
2 diseases, ischemia post myocardial infarction and atherosclerosis; and
3 said composition is selected from derivatives of compounds from a group consisting of
4 piperidine, piperazine and adamantane 

1 22 The method of claim 3 wherein said degenerative diseases comprise stroke, diabetic
2 neuropathy, peripheral neuropathy, Alzheimer's disease, atherosclerosis, ischemia, diabetes,
3 presbycusis, cardiomyopathy and congestive heart failure; and said composition is derived
4 from compounds having terminal nitrogen added molecule substitution with elements selected
5 from a group consisting of glutathione, uric acid, ascorbic acid, taurine, estrogen,
6 dehydroepiandrosterone, probucol, vitamin E, hydroxytoluene, carvidilol, α lipoic acid,
7 tocopherols, ubiquinone, phylloquinone, carotenes, menadione, glutamate, succinate, acetyl-l-
8 carnitine, co-enzyme Q, lazeroids, polyphenolic flavonoids, homocysteine, menaquinone,
9 idebenone, dantrolene and phosphorous.

1 23 The method of Claim 22 wherein said degenerative disease comprises stroke; and said
2 composition consists of uric acid polyamine.

1 24 The method of Claim 22 wherein said ^Bdegenerative disease comprises diabetes; and said
2 composition is derived from compounds selected from a group consisting of phosphorous,
3 taurine, CoEnzyme Q, α lipoic acid, tocopherol, succinate, glutamate and acetyl-l-carnitine
4 polyamines.

1 25 The method of Claim 22 wherein said degenerative disease comprises Alzheimer's disease
2 and presbycusis; and
3 said composition is derived from compounds selected from a group consisting of α lipoic acid
4 and acetyl-l-carnitine polyamines.

1 26 The method of Claim 22 wherein said degenerative disease comprises atherosclerosis; and
2 said composition selected from a group consisting of tocopherol polyamine and coenzyme Q
3 polyamine.

1 27 The method of Claim 22 wherein said degenerative disease comprises ischemia;
2 and
3 said composition is selected from a group consisting of tocopherol polyamine and coenzyme Q
4 polyamine.

1 28 The method of Claim 22 wherein said diseases comprise myocardial degeneration and
2 congestive heart failure; and said composition consists of coenzyme Q polyamine.

1 29. The method of Claim 22 wherein said degenerative diseases comprise cancer; and
2 said composition is taken from a group consisting of cobalt di-homocysteine
3 polyamines.

1 30 The method of Claim 2 wherein said step of converting comprises adjusting the in vivo
2 half life and pharmacokinetic properties of said composition by selective terminal nitrogen
3 substitutions.

1 31 The method of Claim 2 wherein said step of converting comprises adjusting the in vivo
2 half life and pharmacokinetic properties of said composition by addition of side chains on
3 amino or methylene groups. **b**

1 32 The method of Claim 2 wherein said step of selecting comprises:
2 finding the octanol / water coefficients of partition of a series of said compounds; and
3 picking said compound in consideration of its octanol / water coefficient compared to the
4 octanol water coefficients of other compounds in said series.

1 33 The method of Claim 32 wherein said step of picking comprises determining the abilities
2 of said series of compounds to pass through the intestinal, blood brain and blood retinal
3 barriers as a function of their respective octanol / water coefficients; wherein said abilities are
4 determined according to a distribution curve centered about 2 and having a useful range
5 extending towards 0.5 and 4, the numbers being log values.

1 34 The method of Claim 2 wherein said step of selecting comprises;

1 34 The method of Claim 2 wherein said step of selecting comprises;
2 measuring pKas of a list of said compounds; and
3 selecting said compound in consideration of its pKas compared to the pKa's of other
4 compounds on the list.

1 35 The method of Claim 34 wherein said step of selecting comprises;
2 selecting a composition with higher pKas in the treatment a disease characterized by lower
3 tissue pH.

1 36 The method of Claim 35 wherein said diseases include ischemia post myocardial infarction
2 and diabetic ketoacidosis.

1 37 The method of Claim 2 wherein said step of selecting comprises determining the respective
2 likely efficiency of said compounds in consideration of the disease target to be treated and the
3 route of administration.

1 38 The method of Claim 20 wherein;
2 said compound consisting of pyridine tetramine.

1 39 The method of Claim 20 wherein said degenerative disease consists of Alzheimer's
2 disease; and
3 said compound comprises acetyl-L-carnitine polyamine.

1 40 The method of Claim 22 wherein said degenerative disease consists of diabetes; and

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2 said compounds are selected from a group consisting of 2,3,2 piperidine, glutamate polyamine,
3 succinate polyamine, chromium tetramine and vanadyl tetramine and phosphorous polyamine.

1 41 The method of Claim 2 wherein said degenerative diseases comprise peripheral and optic
2 neuropathy; and

3 said compounds comprise taurine polyamine and α lipoic acid polyamines.

1 42 The method of Claim 2 wherein said degenerative diseases comprise glaucoma; and said
2 compounds comprise adamantane 2,3,2 tetramine and adamantane cyclam.

1 43 The method of Claim 3 wherein said degenerative disease comprise presbycusis; and said
2 compounds comprise α lipoic acid polyamine and acetyl-l-carnitine polyamine.

1 44 The method of Claim 4 wherein said composition consists of (2-aminoethyl){3-[(2-
2 aminoethyl)amino]-1-methylbutyl}amine; and said step of admixing a solution comprises
3 preparing said solution by mixing 2,4 dibromopropane and absolute ethanol in a ratio of
4 approximately 1 to 20 per weight.

1 45 The method of claim 44 wherein said step of admixing comprises slowly adding said
2 solution into 1,2-diaminoethane hydrate in a ratio of approximately 44 to 1 per weight.

1 46 The method of claim 45 wherein said step of converting to a tetrahydrochloride salt
2 comprises of adding hydrochloric acid.

1 47 The method of Claim 2 wherein said composition consists of (2-aminoethyl){3-[(2-
2 aminoethyl)amino]-1-methylbutyl}amine; and

3 said step of synthesizing further comprises; the steps of

4 -admixing a solution of an element, taken from a group consisting of 1,3-diaminopropane and
5 N,N-dimethyl-1,3-propanediamine and ethanol into 2-chloromethylpyridine in water;

6 -adjusting the pH of the resulting mixture to 9 by addition of 10% sodium hydroxide;

7 -stirring the mixture at room temperature and maintaining the pH between 8 and 9 by addition
8 of sodium hydroxide over 3 days;

9 -allowing solvents to evaporate; and

10 -extracting residues with CH_2Cl_2 .

1 48 The method of Claim 47 wherein said step of admixing a solution further comprises adding
2 said solution into chloromethyl pyridine in water in a ratio of approximately 5 to 3 per weight
3 wherein said chloromethylpyridine is diluted into water in a ratio of approximately 1 to 5 per
4 weight.

1 49 The method of claim 48 wherein said step of admixing a solution comprises preparing said
2 solution in a ratio of approximately 1 to 50 per weight.

1 50 The method of Claim 49 wherein said steps of synthesizing comprises synthesizing
2 (2-pyridylmethyl){3-[(2-pyridylmethyl)amino]propyl}amine; and
3 said step of admixing a solution further comprises preparing said solution by mixing 1,3-
4 diaminopropane in water with ethanol.

1 51 The method of claim 50 when said step of synthesizing further comprises synthesizing
2 methyl(3-[methyl(2-pyridylmethyl)amino]propyl)(2-pyridylmethyl)amine; and said step of
3 admixing a solution further comprises preparing said solution by mixing N,N-dimethyl-1,3
4 propanediamine in water with ethanol.

1 52 The method of claim 2 wherein said step of synthesizing comprises the steps of a
2 preparation by adding a first solution of 1,3 diaminopropane and absolute ethanol dropwise
3 into a second solution of ethanol and an element taken from a group consisting of 1-
4 (2chloroethyl)piperidine and 1-(2-chloroethylpiperizine) and admixing over approximately 30
5 minutes;
6 stirring said preparation over approximately 24 hours;
7 evaporating the solvents in said preparation;
8 extracting the residue using a volume of CH_2Cl_2 dried over Na_2SO_4 and evaporated to dryness;
9 purifying the resulting composition by converting to its hydrochloride salt by adding
10 hydrochloric acid; and
11 converting said salt to its free amine by treatment with NH_4OH .

1 53 The method of claim 52 wherein said step of mixing a preparation comprises forming said
2 first solution of 1,3 diaminopropane and ethanol in a ratio of approximately 1 to 100 per
3 weight and adding said first solution into said second solution in a ratio of approximately 1 to
4 1 by weight.

1 54 The method of Claim 2 wherein said composition consists of
2 [2-(methylethylamino)ethyl](3-{[2-(methylamino)ethyl]amino}propyl)amine; and said step of
3 synthesizing further comprises; preparing of first mixture of magnesium turnings,
4 1,3-bis-[(2'-aminoethyl)-amino]propane, benzene and acetyl chloride respective approximate
5 percentage of 0.6%, 8.5%, 8.45%, and 6.4% per weight;
6 cooling said first mixture;
7 separating the mixture into a liquid phase and a solid phase;
8 preparing a second mixture by mixing said solid phase with ether;
9 preparing a solution by pouring said second mixture over ice;
10 preparing a third mixture by adding said solution to said liquid phase;
11 washing said third mixture with sodium bicarbonate;
12 washing said third mixture with water.

1 55 The method of Claim 2 wherein said step of synthesizing comprises converting the starting
2 di - or tetramine component, at least one of said components in said compounds to the
3 corresponding N-substituted compound by treatment with an alkyl halide; and
4 purifying said composition by conversion to a salt through addition of hydrochloric acid.

1 56 The method of Claim 2 wherein said composition consists of (2-aminoethyl){3-[(2-
2 aminoethyl)methylamino]propyl}methylamine, and
3 said step of synthesizing further comprises:
4 preparing a first solution of N,N-dimethyl-1,3-propanediamine and ethanol in a ratio of
5 approximately 1 to 50 per weight;

6 preparing a second solution of 2-chloroethylamine and ethanol in a ratio of approximately 1 to
7 17 per weight;
8 combining said first and second solutions into a third solution;
9 stirring said third solution at room temperature for approximately 20 hours;
10 evaporating solvents in said third solution; and
11 extracting residues in said solution with a volume of CH_2Cl_2 .

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1 57 The method of Claim 2 wherein said composition consists of
2 [2-(bicyclo[3.3.1]non-3-ylamino)ethyl](3-{2-(bicyclo[3.3.1]non-3-
3 ylamino)ethyl}amino)propyl)amine, and said step of synthesizing further comprises heating
4 for approximately 6 hours at 215°C a mixture of 1-bromoadamantane and 2,3,2-tetramine in a
5 mol ratio of approximately 1 to 5;
6 admixing said mixture into a solution of 2NHCl and ether having a ratio of approximately 1.25
7 to 1 per weight, in a ratio of approximately 1 to 9 per weight;
8 separating the aqueous layer and alkalinizing said layer in a volume of 50% aqueous NaOH ;
9 extracting with ether;
10 drying the extract over K_2CO_3 ; and
11 evaporating to an oil.

1 58 The method of Claim 2 wherein said composition consists of [2-
2 (methylethylamino)ethyl](3 {2-(methylamino)ethyl}amino)propyl)amine; and
3 said methylating step of synthesizing further comprises;
4 methylating terminal nitrogens of 2,3,2 tetramine by refluxing in the presence of benzene and
5 acetyl chloride.

59 The method of Claim 58 wherein said step of synthesizing further comprises;
preparing a first mixture of magnesium turnings;
of 1,3-bis-[(2'-aminoethyl)-amino]propane, benzene and acetyl chloride respective
approximate percentage of 0.6%, 8.5%, 8.45%, and 6.4% per weight;
cooling said first mixture;
separating the mixture into a liquid phase and a solid phase;
preparing a second mixture by mixing said solid phase with ether;
preparing a solution by pouring said second mixture over ice;
preparing a third mixture by adding said solution to said liquid phase;
washing said third mixture with sodium bicarbonate;
washing said third mixture with water;
drying said third mixture over CaCl_2 ;
filtering said third mixture;
preparing a fourth mixture of said third mixture sodium hydride and N,N-dimethylformamide
in a ratio of approximately 2.5, 1 and 37.5 respectively per weight;
heating said fourth mixture under N_2 at approximately 60°C for about three hours;
treating said fourth mixture with approximately $\frac{1}{4}$ its volume of iodomethane;
stirring said treated fourth mixture at 50°C for approximately 24 hours;
quenching said treated fourth mixture with 95% ethanol;
removing volatiles at reduced pressure;
watering with addition of approximately $\frac{1}{2}$ volume of water;
extracting organic products with approximately three $\frac{1}{2}$ volumes of chloroform;
washing said organic products with water and NaCl ;
drying said organic products over anhydrous sodium sulfate;



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25 concentrating into an oil;
26 purifying said oil by flash chromatography with ¼ hexanes-ethyl acetate as eluent into an
27 acetylated oil of said composition;
28 forming a solution of said acetylated oil, potassium hydroxide, methanol and water in
29 respective proportions of 1, 3, 23 and 5 per weight respectively;
30 heating said solution under reflux for about 24 hours;
31 removing methanol at reduced pressure;
32 extracting into ether;
33 washing with NaCl;
34 drying over sodium sulfate;
35 concentrating under vacuum;
36 purifying by flash chromatography; and
37 evaporating solvents.

1 60 The method of Claim 2 wherein said composition consists of [2-(dimethylamino)ethyl](3-
2 {[2-(dimethylamino)ethyl]methylamino}propyl)methylamine; and
3 said steps of synthesizing further comprises;
4 refluxing for about 20 hours a solution of 2,3,2 tetramine, formic acid and 37% formaldehyde
5 and water in a weight proportions of approximately 1,10,10 and 1 respectively;
6 evaporating solvents from said solution;
7 making said solution basic by addition of NaOH; and
8 extracting residues with 3 times 1½ volume of CH₂Cl₂.

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61 The method of Claim 2 wherein said composition consists of 2-[3-(2-aminoethylthio)propylthio]ethylamine; and
said step of synthesizing further comprises:
preparing a first solution of 1,3-dimercaptopropane and water in a weight ratio of about 1 to 50;
preparing a second solution of NaOH and water in a weight ratio of about 1.5 to 10;
forming a first mixture by mixing said first and second solutions in a weight ratio of about 5 to 1;
forming a third solution of 2-chloroethylamine and ethanol in a weight ratio of about 8.5 to 1;
admixing said solution into said mixture in a ratio of about 1 to 3.8;
refluxing said mixture over approximately 8 hours;
evaporating solvents from said refluxed mixture;
extracting residues with CH_2Cl_2 .

62 The method of Claim 2 wherein said composition consists of:
1,4,8,11-tetraaza-1,4,8,11-tetramethylcyclotetradecane; and
said steps of synthesizing comprises:
refluxing for about 18 hours a solution of cyclam, formic acid, 37% formaldehyde and water in weight proportions of approximately 13 3.3, 4.5 and 1 respectively;
adding water to said solution in a weight ratio of approximately 0.5 to 1;
cooling said solution to about 5°C ;
adjust the pH of said solution to above 12 with NaOH;
extracting the solution with CH_2Cl_2 ;

1 63 The method of Claim 2 wherein said composition consists of 1,4,8,11-tetraaza-1,4,8,11-
2 tetra(2-piperidylethyl)cyclotetradecane; and said step of synthesizing further comprises:
3 preparing a first solution of cyclam and CH_2Cl_2 in a weight ratio of approximately 1 to 50;
4 preparing a second solution of NaOH and water in a weight ratio of approximately 1 to 31;
5 preparing a mixture of said first and second solution in a weight ratio of approximately 1 to 1;
6 preparing a third solution of 1-(2-chloroethyl)piperidine and CH_2Cl_2 in a weight ratio of
7 approximately 1 to 14;
8 adding said third solution dropwise into said mixture in a weight ratio of about 1 to 2;
9 stirring said mixture over about 24 hours;
10 evaporating solvents; and
11 extracting residues with CH_2Cl_2 .

1 64 The method of Claim 2 wherein said composition consists of 1,4,8,11-tetraaza-1,4,8,11 -
2 tetrabicyclo[3.3.1]non-3-ylcyclotetradecane; and
3 said step of synthesizing further comprises:
4 forming a first solution of cyclam and ethanol in a weight ratio of approximately 1 to 100;
5 forming a second solution of 1-bromoadamantane and ethanol in a weight ratio of 1 to 23;
6 forming a mixture by adding said second solution dropwise into said first solution in a weight
7 ratio of about 1 to 1, over 30 minutes;
8 heating said mixture to reflux over about 20 hours;
9 evaporating said solution under reduced pressure; and
10 extracting residue from said solution with CH_2Cl_2 ;

1 65 The method of Claim 2 wherein said composition consists of

1,4,8,11-tetraaza-1,4,8,11-tetraethylcyclotetradecane; and

said step of synthesizing further comprises:

forming a solution of cyclam and DMF in a weight ratio of approximately 1 to 50;

admixing under stirring small portions of NaH in a weight ratio of about 1 to 12.5;

heating said solution for about three hours at about 60°C;

admixing iodoethane in a single portion into said solution in a weight ratio of about 1 to 17.5;

heating said solution at about 60°C over about 18 hours;

quenching the solution with about 95% ethanol;

extracting residue with CH₂Cl₂.

66 The method of Claim 2 wherein said composition consists of N,N'-(2'
dimethylphosphinoethyl)-propylenediamine; and the step of synthesizing further comprises:
incorporating phosphorus into a molecule of propylenediamine in place of two of its nitrogen
atoms by addition and reduction reactions.

67 The method of Claim 66 wherein said step of incorporating comprises:

preparing a first solution by dissolving propylenediamine into ethanol in a weight ratio of
about 1 to 50;

admixing dimethylvinylphosphine sulfide into said solution in a weight ratio of about 1 to 22;

heating at reflux said solution for about 72 hours;

evaporating solvents under reduced pressure, leaving a residue.

68 The method of Claim 67 wherein said step of incorporating further comprises:

dissolving said residue in chloroform;

3 washing said residue with NaOH; and

4 drying said residue over MgSO_4 .

1 69 The method of Claim 68 wherein said step of synthesizing further comprises:

2 removing solvents in said residue under reduced pressure to yield an oil,

3 crystallizing said oil with ethyl acetate;

4 preparing a suspension of LiAlH_4 in dry dioxane in a weight ratio of about 1 to 100;

5 admixing said oil into said suspension;

6 to yield a mixture;

7 refluxing said mixture for about 36 hours;

8 cooling said mixture; and

9 adding a solution of dioxane in water and NaOH into said mixture.

1 70 The method of Claim 2 wherein said diseases consist of diabetes and abnormal low density
2 lipoprotein (LDL) to high density lipoprotein (HDL) ratio and said composition is selected

3 from a group consisting of vanadyl 2,3,2-tetramine and chromium 2,3,2-tetramine; and

4 said step of synthesizing further comprises reacting a metallic salt with 2,3,2-tetramine in an
5 ethanol solution.

1 71 The method of Claim 70 wherein said step of reacting comprises:

2 forming a first solution of 2,3,2 tetramine in ethanol in a weight ratio of about 1 to 20;

3 forming a second solution of vanadyl acetylacetonate in ethanol in a weight ratio of about 1 to
4 275;

5 admixing said second solution into said first solution in a volume ratio of about 1 to 1; and

6 refluxing said solution for almost 30 minutes.

1 72 The method of Claim 70 wherein said step of reacting further comprises:

2 preparing a first solution of 2,3,2-tetramine in ethanol in a weight ratio of about 1 to 20;

3 preparing a second solution of chromium (III) nitrate in ethanol in a weight ratio of about 1 to

4 80;

5 admixing said second solution into said first solution in a volume ratio of about 1 to 1; and

6 refluxing said solution for about 30 minutes.

1 73 The method of Claim 55 wherein said step of converting comprises using amines to attach

2 alkyl halide in a nucleophilic substitution of N atoms.

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